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Perioperative Care of an Adolescent With 11-Beta-Hydroxylase Deficiency

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Abstract

Congenital adrenal hyperplasia (CAH) is the result of an autosomal recessive disorder affecting one of the several steps required for the synthesis of cortisol from cholesterol by the adrenal cortex. 11β-hydroxylase deficiency accounts for 5-8% of all cases of CAH with an incidence estimated at 1 in 100,000 - 200,000 newborns. We present a 14-year-old girl with CAH due to 11β-hydroxylase deficiency who presented for surgical treatment of virilization. The perioperative care of patients with CAH should address issues related to the deficient and excessive production of specific mineralocorticoids and corticosteroids by the adrenal cortex. The authors discuss the perioperative implications of the disorder and review previous reports of anesthetic care for such patients.

Keywords: Congenital adrenal hyperplasia; 11-beta-hydroxylase deficiency; Hypotension; Anesthesia; Adrenal insufficiency

Introduction

Congenital adrenal hyperplasia (CAH) is the result of an autosomal recessive disorder affecting one of the several steps required for the synthesis of cortisol from cholesterol by the adrenal glands. The most common form of CAH, accounting for more than 90% of cases, results from the deficiency of the enzyme, 21-hydroxylase. This enzymatic defect results in the deficient production of both corticosteroids and mineralocorticoids leading to poor feeding, failure to thrive, Addisonian crisis, salt loss, and hyperkalemia during the newborn period. The impaired production of cortisol leads to excessive release of adrenocorticotropic hormone (ACTH) which results in adrenal hyperplasia and excessive synthesis of adrenal androgens including dehydroepiandrosterone, androstenedione, and especially testosterone. These androgens result in the phenotypic manifestations of the disorder which includes partial virilization and ambiguous genitalia of genetically female infants, childhood virilization of both genders, and rarer cases of virilization or infertility of adolescent and adult women.

CAH due to 11β-hydroxylase deficiency accounts for 5-8% of all cases with an incidence estimated at 1 in 100,000 - 200,000 newborns. The gene is located on the long arm of chromosome 8. This condition is more common in Moroccan Jews living in Israel, occurring in approximately 1 in 5,000 - 7,000 newborns. 11β-hydroxylase mediates the final step of the glucocorticoid pathway, producing cortisol from 11-deoxycortisol. It also catalyzes the conversion of 11-deoxycorticosterone (DOC) to corticosterone in the mineralocorticoid pathway. The diagnosis of 11β-hydroxylase deficient CAH is confirmed by the demonstration of marked elevations of the substrates of the 11β-hydroxylase enzyme including 11-deoxycortisol and 11-DOC. In these patients, surgical intervention is required to correct the virilizing effects of the over-production of adrenal androgens. We present a 14-year-old girl with CAH due to 11β-hydroxylase deficiency who presented for surgical treatment of virilization. The perioperative implications of the disorder are discussed and previous reports of anesthetic care for patients with CAH are reviewed.

Case Report

Institutional Review Board approval for isolated case reports is not required by Nationwide Children's Hospital. This patient was cared for during a surgical mission trip to San Pedro Sula, Honduras sponsored by International Volunteers in Urology (Salt Lake City, UT) and the Ruth Paz Foundation (San Pedro Sula, Honduras).

The patient was a 14-year-old, 62 kg adolescent who pre-

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sented to clinic for evaluation and treatment of severe virilization. Past medical history was notable for largely untreated congenital adrenal hyperplasia due to 11β-hydroxylase deficiency and hypertension. Medications included prednisone 20 mg orally once a day and candesartan (an angiotensin receptor blocking agent) 12 mg orally twice a day for hypertension. She reported no known drug or food allergies. Preoperative physical examination was notable for extensive masculinization, but was otherwise unremarkable. Due to the relative lack of medical care she had received, laboratory values and medical records were unavailable. However, preoperative serum electrolytes, blood urea nitrogen, and creatinine were within normal limits. Preoperative vital signs were as follows: blood pressure (BP) 123/67 mm Hg, heart rate 92 beats per minute, respiratory rate 14 breaths per minute, and oxygen saturation 99% on room air.

The patient was scheduled for vaginal reconstruction and feminizing genioplasty (clitoral recession and perineal vaginoplasty using partial urogenital sinus mobilization). The patient was held *nil per os* on the day of surgery. A 22-gauge peripheral intravenous catheter was placed by the hospital staff prior to the patient's arrival in the operating room. Standard American Society of Anesthesiologists (ASA) monitors were placed and oxygen was administered via face mask. Hydrocortisone 100 mg was administered intravenously prior to anesthetic induction. Intravenous induction was performed with fentanyl 100 µg, lidocaine 60 µg, and propofol 200 mg. A size 3 laryngeal mask airway was placed atraumatically and proper positioning was verified. Anesthesia was maintained with 1.5% isoflurane in 100% oxygen. The patient was positioned in the right lateral decubitus position for placement of a caudal epidural catheter for postoperative pain control. The procedure was performed under standard sterile conditions. The caudal space was easily accessed with a 17-gauge, 3.5″ Tuohy needle and a 19-gauge epidural catheter was threaded such that the tip of the catheter was at approximately the $L_{4\text{-}5}$ interspace. Aspiration of the catheter was negative for blood and cerebrospinal fluid. A test dose of 3 mL of 0.25% bupivacaine with epinephrine (1:200,000) was negative. The patient was then placed in the lithotomy position for surgery and the epidural catheter was dosed with 15 mL of 0.5% bupivacaine. Cefazolin (2,000 g) was administered intravenously for surgical site infection prophylaxis. At the time of surgery start, her vital signs were as follows: BP 112/70 mm Hg, heart rate 87 beats per minute, respiratory rate 12 breaths per minute, and oxygen saturation 100% with an FiO_2 of 1.0.

There was minimal hemodynamic change on surgical incision with an isoflurane concentration of 1% demonstrating adequate epidural anesthesia. Approximately 15 min after surgical incision, the BP declined to 70/42 mm Hg. As the BP was rechecked, a fluid bolus of isotonic saline was administered. The subsequent BP was 50/32 mm Hg, so epinephrine 10 µg was administered intravenously (phenylephrine and ephedrine are not available in Honduras). This had minimal efficacy in increasing the BP, and escalating bolus doses of epinephrine were required (100 µg per dose). The surgeons were notified, and other causes of severe hypotension (anaphylaxis, hypovolemia, medication error, pulmonary embolus, and myocardial ischemia) were considered and ruled out. The working diagnosis was adrenal insufficiency with superimposed vasoplegia secondary to angiotensin receptor blocker therapy. An additional dose of hydrocortisone (100 mg) was administered intravenously. Because we did not have access to contemporary anesthesia equipment including an infusion pump, we improvised by adding 1 mg of epinephrine to 1 L of normal saline. The infusion was titrated to effect by using the roller clamp which resulted in acceptable BP control (75 - 100/40 - 60 mm Hg). A second peripheral intravenous catheter was placed to allow for additional fluid and medication administration. An additional 2,000 mL of isotonic crystalloid was also administered. Approximately 1.5 h into the surgery, the patient showed signs of receding epidural blockade, so the epidural was redosed with 10 mL of 0.25% bupivacaine 0.25% with epinephrine (1:200,000) plus clonidine 50 µg. Over the course of the operative procedure, the rate of epinephrine infusion was slowly decreased and then discontinued 30 - 60 min prior to the end of the surgical procedure. The remainder of the surgical course was unremarkable. The procedure, in its entirety, lasted approximately 5 h. Upon emergence, the LMA was removed. The patient's hemodynamic status remained stable in the recovery room without further fluid or vasopressor support. The patient denied pain when questioned in the recovery room. That evening, her routine oral dose of candesartan was restarted and the next day, her usual oral prednisone therapy was restarted. The epidural catheter was left in place and dosed at 8 - 12 h intervals to provide ongoing postoperative analgesia. The remainder of the postoperative course was unremarkable.

Discussion

The perioperative care of patients with CAH should address issues related to the deficient and excessive production of specific mineralocorticoids and corticosteroids by the adrenal cortex. The mineralocorticoid manifestations of severe 11β-hydroxylase deficiency in CAH can be biphasic, changing from a salt-wasting presentation in early infancy to excessive production resulting in hypertension in childhood and adolescence. Although salt-wasting in early infancy is rare, it occasionally occurs in 11β-hydroxylase CAH because of the impaired production of aldosterone coupled with the normal inefficient renal sodium conservation of neonates and infants. The clinical manifestations are similar to those of the severe forms of 21-hydroxylase deficient CAH, including poor weight gain and vomiting in the first weeks of life, progressing to dehydration, hyponatremia, hyperkalemia, and metabolic acidosis which result in death if not effectively diagnosed and treated [1, 2]. Therapy includes the administration of intravenous normal saline to restore intravascular volume, dextrose to correct hypoglycemia, and the administration of replacement doses of hydrocortisone. Long term treatment with exogenous mineralocorticoids (fludrocortisone) replacement is usually not necessary.

Despite the inefficient production of aldosterone, the more characteristic mineralocorticoid effect of the 11β-hydroxylase of CAH is hypertension. Progressive adrenal hyperplasia due to persistent elevation of ACTH results in the excessive production of 11-DOC by early to mid-childhood. Although DOC

is a weak mineralocorticoid when compared to aldosterone, the plasma concentrations are high enough to result in the classic effects of mineralocorticoid excess including salt retention, volume expansion, and hypertension. Approximately two-thirds of patients with CAH due to 11β-hydroxylase deficiency will manifest hypertension, typically developing within the first year or two of life. Excessive DOC also results in hypokalemia and alkalosis. The latter resulting from the excretion of hydrogen ion to maintain electrical neutrality in the kidneys as sodium is reabsorbed. Given these concerns, the preoperative assessment of electrolytes and acid-base status is suggested. The acid-base status as assessed by the serum bicarbonate can be used to generally assess the efficacy of corticosteroid replacement therapy [3]. Perioperative corticosteroid therapy is similar to that of 21-hydroxylase deficient CAH except that mineralocorticoids need not be replaced. The primary therapy of 11β-hydroxylase deficiency is lifelong glucocorticoid replacement in doses to prevent adrenal insufficiency and suppress excessive ACTH production. Suppression of ACTH results in limitation of excessive mineralocorticoid and androgen production.

Perioperative corticosteroid therapy is recommended to avoid cardiovascular compromise due to the stress of surgery and anesthesia [4, 5]. While the time-honored therapy of patients on chronic glucocorticoid therapy has been to administer "stress doses" during the perioperative period with dosing calculated to match the maximum adrenal output (6 - 8 times the basal secretion), the need for such therapy has recently been questioned with the suggestion that many patients require only the continuation of maintenance corticosteroid therapy without stress dosing [4, 5]. This practice has been suggested given the potential adverse effect profile of high dose corticosteroid therapy including immune suppression, increased incidence of surgical site infections, delayed wound healing, hyperglycemia, and gastric bleeding [6-8]. In our patient, our plan was to administer a single preoperative dose of hydrocortisone; however, a second dose was administered intraoperatively due to the excessive hypotension. As the patient's postoperative course was unremarkable, her routine dose of prednisone was restarted the next morning and no further supplementation was provided.

Significant perioperative concerns may exist related to long term glucocorticoid therapy. Although necessary, chronic glucocorticoid therapy may result in hypertension related to abnormal renal sodium homeostasis, cataracts, osteoporosis, impaired wound healing, disordered glucose homeostasis, and cataract formation [6, 8, 9]. A large meta-analysis demonstrated that patients on chronic glucocorticoid therapy were 2.2 times more likely to be hypertensive, regardless of the duration of therapy [10]. As such, perioperative glucose monitoring is suggested in patients receiving chronic corticosteroid therapy. Treatment of hyperglycemia, depending on its magnitude, may also be indicated. In the diabetic patient with absolute or relative insulin deficiency, surgical procedures and the associated stress response can lead to marked hyperglycemia and even diabetic ketoacidosis [11]. Hyperglycemia also can impair wound healing and increase the risk of surgical site infections [12-14]. Although clinical studies have not consistently demonstrated a significant relationship between perioperative gly-

Table 1. Previous Reports of Anesthesia in Patients With Congenital Adrenal Hyperplasia

Author and reference	Patient age	Hyperglycemia	Hypertension	Co-morbid conditions	Medications	Lab results	Surgical procedure	Anesthetic	Intraoperative problems
Bansal et al [28]	3 years	No	No	Maroteaux-Lamy disease (MPS IV)	Hydrocortisone 10 mg/day, prednisolone 1.5 mg/day	Normal	MRI of the brain	General inhalational anesthesia with sevoflurane using an LMA	None
Okamoto et al [29]	12 years	No	Yes, severe	None	Spironolactone (dose unspecified)	Not reported	Genitoplasty	General inhalational anesthesia with nitrous oxide and sevoflurane; epidural catheter	Severe hypertension (sBP > 180 mm Hg)
Van Obbergh et al [30]	6 years	No	No	Xp21 deletion, DMD, glycerol kinase deficiency	Hydrocortisone (dose unspecified)	Not reported	Bilateral hip osteotomies	TIVA with remifentanil, bolus doses of thiopentone and endotracheal intubation, epidural catheter	None
Yamashita [31]	8 weeks	No	No	None	Hydrocortisone 15 mg twice a day	Potassium 5.6 mmol/L, sodium 132 mmol/L	Genitoplasty	Chloral hydrate, spinal anesthesia with tetracaine	None

MPS: mucopolysaccharoidosis; GA: general anesthesia; LMA: laryngeal mask airway; TIVA: total intravenous anesthesia; DMD: Duchenne muscular dystrophy; sBP: systolic blood pressure.

cemic control and short-term risk of infection or morbidity, tight glucose control has been recommended by some investigators with a demonstration of decreased perioperative morbidity [15-17]. For major surgical procedures, a continuous intravenous infusion of insulin has been shown to be superior to subcutaneous injections in achieving perioperative optimal glycemic control [18-20]. Hyperglycemia may also result in glucosuria, polyuria, and electrolyte disturbances during the perioperative period.

As noted in our patient, 11β-hydroxylase deficiency frequently results in hypertension requiring therapy. While continuation of anti-hypertensive medications is generally recommended, the perioperative administration of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) may result in excessive intraoperative hypotension [21, 22]. Anecdotal success has been reported with the use of vasopressin in cases refractory to direct acting adrenergic agonists (epinephrine, phenylephrine) [23]. Given these concerns, it is generally recommended to hold ACE inhibitors and ARB agents the morning of surgery in adults; however, no consensus has been reached regarding the recommendations for the pediatric population. Although various intraoperative etiologies were considered for the hypotension that occurred in our patient, we thought that the most likely etiologies included the perioperative administration of her routine anti-hypertensive agent combined with the sympathectomy induced by the caudal epidural anesthesia. Restoration of adequate BP was accomplished by the administration of isotonic fluids and the use of a vasopressor agent, epinephrine.

To date, there are limited previous reports in the literature regarding the perioperative care of patients with CAH including those in non-English journals [24-26]. The significant implications of CAH are illustrated by reports of death or malignant ventricular arrhythmias in undiagnosed newborns [2, 27]. Previous reports from the English literature are summarized in Table 1 [28-31]. Both volatile agents and total intravenous anesthesia have been used successfully. One report outlines the use of spinal anesthesia. No major intraoperative problems have been reported.

In summary, we present the perioperative care of a 14-year-old girl with CAH due to 11β-hydroxylase deficiency who presented for surgical treatment. Given the potential for electrolyte disturbances related to the primary disease process or its treatment, preoperative evaluation of electrolytes is suggested. Given the effects of corticosteroids on sodium and hydrogen ion homeostasis, the acid-base status can be used as a surrogate for the efficacy of corticosteroid replacement. While perioperative corticosteroid therapy is mandatory, controversy exists as to whether this should include continuation of the routine maintenance doses of corticosteroids or the administration of a perioperative "stress dose". Perioperative glucose homeostasis can be altered by corticosteroid therapy, pain, and the surgical stress response. As was used in our patient, neuraxial analgesia (caudal epidural) may be more effective in blunting the surgical stress response and its impact on glucose homeostasis than intravenous opioid therapy. Patients with 11β-hydroxylase deficiency may require chronic therapy for hypertension. Perioperative hemodynamic instability may occur related to the perioperative administration of ACE inhibitors and ARB agents. Refractory cases may require the administration of vasopressin to restore hemodynamic stability.

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